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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/665,005	09/19/2003	Kamil Paruch	OC01625K	5836

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SCHERING-PLOUGH CORPORATION  
PATENT DEPARTMENT (K-6-1, 1990)  
2000 GALLOPING HILL ROAD  
KENILWORTH, NJ 07033-0530

EXAMINER

RAO, DEEPAK R

ART UNIT	PAPER NUMBER
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1624

DATE MAILED: 03/12/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

**Office Action Summary**

Application No.

10/665,005

Applicant(s)

PARUCH ET AL.

Examiner

Deepak R Rao

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 19 September 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-30 are pending in the application.
- 4a) Of the above claim(s) 3, 4, 9 and 13-16 are withdrawn from consideration.
- 5) ☒ Claim(s) 18 is/are allowed.
- 6) ☒ Claim(s) 1, 2, 5-8, 10-12, 17 and 19-30 are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)  
Paper No(s)/Mail Date 121503.
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date. \_\_\_\_\_.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: \_\_\_\_\_.

### **DETAILED ACTION**

Claims 1-30 are pending in this application.

#### ***Election/Restrictions***

Claims 1-30 are generic to a plurality of disclosed patentably distinct species comprising the species disclosed in the examples. Applicant is required under 35 U.S.C. 121 to elect a single disclosed species, even though this requirement is traversed.

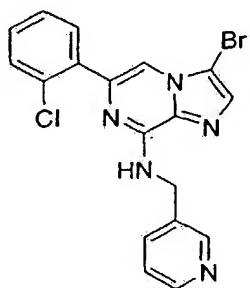
The compounds are structurally dissimilar such that a reference anticipating a compound may not render the remaining compounds obvious. 37 CFR 1.141(a) provides that two or more independent and distinct inventions may not be claimed in one application, whether or not the misjoinder occurred in one claim or more than one claim. Restriction is going to be exercised where independent and distinct inventions are presented in one Markush grouping. Independent means when the compound is being made and/or used alone, not in combination with other compounds of the Markush expression. Restriction is considered proper in Markush claims where the members are so diverse and unrelated that a prior art reference anticipating the claim with respect to one of the members, would not render the claims obvious under 35 U.S.C. 103 with respect to the other members. Therefore, what should be considered for patentable distinctness is the compound as a whole. Each of the species based on the various substituents are independently classified into different class/subclasses, thereby requiring consideration of thousands of patent documents. Further, these compounds require separate searches in the literature and therefore, involve burdensome search.

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Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

During a telephone conversation with Mr. Palaiyur Kalyanaraman on March 9, 2004 a provisional election was made with traverse to prosecute the species of Example 21 (page 38) (depicted below for convenience). Affirmation of this election must be made by applicant in replying to this Office action.

Elected species:



The elected species represents a compound of formula III



Formula III

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wherein:

R is 2-chlorophenyl;

R<sup>1</sup> is H;

R<sup>2</sup> is Br; and

R<sup>3</sup> is (pyrid-3-yl)methyl.

The elected species reads on claims 1-2, 5-8, 11 and 17-30.

Applicant is reminded of the election of species guidelines provided in MPEP § 803.02, which are followed for examination. Portion from MPEP is provided here for convenience:

As an example, in the case of an application with a Markush-type claim drawn to the compound C-R, wherein R is a radical selected from the group consisting of A, B, C, D and E, the examiner may require a provisional election of a single species, CA, CB, CC, CD or CE. The Markush-type claim would then be examined fully with respect to the elected species and any species considered to be clearly unpatentable over the elected species. If on examination the elected species is found to be anticipated or rendered obvious by prior art, the Markush-type claim and claims to the elected species shall be rejected, and claims to the non-elected species would be held withdrawn from further consideration. As in the prevailing practice, a second action on the merits on the elected claims would be final.

On the other hand, should no prior art be found that anticipates or renders obvious the elected species, the search of the Markush-type claim will be extended. If prior art is then found that anticipates or renders obvious the Markush-type claim with respect to a nonelected species, the Markush-type claim shall be rejected and claims to the nonelected species held withdrawn from further consideration. The prior art search, however, will not be extended unnecessarily to cover all nonelected species. Should applicant, in response to this rejection of the Markush-type claim, overcome the rejection, as by amending the Markush-type claim to exclude the species anticipated or rendered obvious by the prior art, the amended Markush-type claim will be reexamined. The prior art search will be extended to the extent necessary to determine patentability of the Markush-type claim. In the event prior art is found during the reexamination that anticipates or renders obvious the amended Markush-type claim, the claim will be rejected and the action made final. Amendments submitted after the final rejection further restricting the scope of the claim may be denied entry.

The elected species was not found in the prior art search and as per the guidelines above, the examination was expanded to compounds of **formula III** wherein **R<sup>3</sup> is (pyridyl)methyl** and **R<sup>2</sup> is as defined in the claims while retaining the definitions of R and R<sup>1</sup> as in the elected species** and art was found. Claims 3-4, 9, and 13-16 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected species. All other definitions of the variables R, R<sup>1</sup> and R<sup>3</sup> from the generic claims 1-2, 5-8, 10-12 and 19-30;

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and the species from claims 17-18 that do not fall in the above described subgenus are withdrawn from consideration, pursuant to 37 CFR 1.142(b) as being drawn to non elected subject matter.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

### ***Specification***

The disclosure is objected to because of the following informalities:

Pages 50-56, several structural formulae in Table 4 are not completely legible. Substitute pages having clear structures may be needed for the disclosure.

Appropriate correction is required.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 19-20, 22-23 and 25-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting CDK2 and/or a method of treatment of specific cancers (recited in claim 24), does not reasonably provide enablement for inhibiting all types of cyclin dependent kinases or for the treatment of all other diseases

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embraced by the instant claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The instant claims are drawn to "a method of inhibiting one or more cyclin dependent kinases" and "a method of treating one or more diseases associated with cyclin dependent kinase" which according to specification are drawn to a therapeutic use, e.g., in treating proliferative diseases, autoimmune diseases, viral diseases, etc. (see page 20). First, the instant claims cover 'diseases' that are known to exist and those that may be discovered in the future, for which there is no enablement provided. Test assays and procedures using CDK2 containing cells are provided in the specification pages 61-62, related to CDK2 inhibition, wherein the CDK inhibitory activity data (in terms of  $IC_{50}$ ) for some of the compounds of the invention is provided in Table 7, however, there is nothing in the disclosure regarding how this *in vitro* data correlates to the treatment of the disorders of the instant claims. The disorders encompassed by the instant claims include proliferative disorders or cancers which have been proven to be extremely difficult to treat. Further, there is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

Further, there is no disclosure regarding how the patient in need of such specific kinase inhibiting activity is identified and further, how types of proliferative diseases are treated. See MPEP § 2164.03 for enablement requirements in cases directed to structure-specific arts such as

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the pharmaceutical art. Receptor activity is generally unpredictable and highly structure specific area, and the data provided of the single compound is insufficient for one of ordinary skill in the art in order to extrapolate to the other compounds of the claims. It is inconceivable as to how the claimed compounds can treat the extremely difficult diseases embraced by the instant claims. The state of the art is indicative of the unpredictability of the therapeutic approach based on kinase inhibiting activity. Regarding CDK mechanism, Blain et al. (J. of Biol. Chem.) report that "their specific functions are still poorly understood" (see page 25863, col. 1). Also, LuValle et al. (Frontiers in Bioscience) express that "detailed analyses of these pathways are necessary for a complete understanding of chondrocyte proliferation and differentiation" (see page 5, section 4). This is clearly indicative of the fact that the therapeutic role of these kinase inhibitors is very speculative.

A 'proliferative disorder' is anything that causes abnormal tissue growth. That can be growth by cellular proliferation more rapidly than normal, or continued growth after the stimulus that initiated the new growth has ceased, or lack (partial or complete) of structural organization and/or coordination with surrounding tissue. It can be benign or malignant. Thus, such term covers not only all cancers, but also covers precancerous conditions such as lumps, lesions, polyps, etc. No compound has ever been found to treat cancers of all types generally. Since this assertion is contrary to what is known in medicine, proof must be provided that this revolutionary assertion has merits. The existence of such a "silver bullet" is contrary to our present understanding of oncology. Cecil Textbook of Medicine states that "each specific type has unique biologic and clinical features that must be appreciated for proper diagnosis, treatment and study" (see the enclosed article, page 1004). Different types of cancers affect different

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organs and have different methods of growth and harm to the body. Also see *In re Buting*, 163 USPQ 689 (CCPA 1969), wherein 'evidence involving a single compound and two types of cancer, was held insufficient to establish the utility of the claims directed to disparate types of cancers'. Thus, it is beyond the skill of oncologists today to get an agent to be effective against cancers generally.

Applicants have not provided any competent evidence or disclosed tests that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970).

(Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements).

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

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The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 25-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 25 recites the limitation "or a pharmaceutically acceptable salt or solvate thereof" in lines 4-5. There is insufficient antecedent basis for this limitation in claim 1 on which claim 25 depends from. Claim 1 does not include 'a pharmaceutically acceptable salt or solvate' of compound of formula III.

### ***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-2, 5-8, 10-12, 17 and 19-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over Burns et al., WO 02/060492. The reference teaches a generic group of imidazo[1,2-a]pyrazine compounds that are useful as therapeutic agents having kinase inhibitory activity, see formula II in page 10 and the corresponding species in Table 7, particularly compound 57 (page 56, last compound) and the activity in page 16, starting at line 19. The instant claims recite that R<sup>2</sup> is alkyl, e.g., methyl, as compared to the reference compound which is unsubstituted at the analogous position. Since the instant compounds differ by having a methyl group in place of the hydrogen disclosed for reference compounds (i.e., differing by a -CH<sub>2</sub> group), the instantly claimed compounds are homologs of the reference compound. One having ordinary skill in the art would have been motivated to prepare the instantly claimed compounds because such structurally homologous compounds would be expected to possess similar utilities. It has been held that compounds that are structurally homologous to prior art compounds are prima facie obvious, absent a showing of unexpected results. *In re Haas*, 60 USPQ 544 (CCPA 1944); *In re Henze*, 85 USPQ 261 (CCPA 1950).

### ***Duplicate Claims***

Applicant is advised that should claim 1 be found allowable, claim 30 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Claim 30 does not further

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limit the compound of claim 1 because the compound of claim 1 is assumed to be a pure compound.

***Allowable Subject Matter***

Claim 18 is allowed. The references of record do not teach or fairly suggest the claimed compounds.

Receipt is acknowledged of the Information Disclosure Statement filed on December 15, 2003 and a copy is enclosed herewith.

***Conclusion***

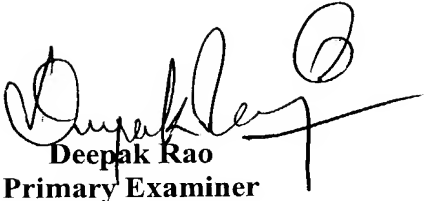
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Tuesday-Friday from 6:30am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Mukund Shah, can be reached on (571) 262-0674. If you are unable to reach Dr. Shah within a 24 hour period, please contact James O. Wilson, Acting-SPE of 1624 at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

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**Deepak Rao**  
**Primary Examiner**  
**Art Unit 1624**

March 10, 2004